

REMARKS

Applicants appreciate Examiner's determination that Claims 2-4, 10-21 and 27 are allowable.

Claims 24-26 were rejected under 35 USC §112, first paragraph, as lacking enablement. Claims 1, 6, 8, 22 and 28-29 were rejected under 35 USC §102(b) as being anticipated by Giraldi et al. US 3,074,943. Claims 1, 5-8, 22 and 28-29 were rejected under 35 USC §102(b) as being anticipated by Cutler et al. US 3,097,205. Claims 1, 6, 23 and 28-29 were rejected under 35 USC §102(b) as being anticipated by Cutler et al. US 3,209,003. Claims 1, 6, and 8-9 were rejected under 35 USC §103(a) as being unpatentable over Newton et al. US 5,062,882. Claims 1 and 6 were rejected under 35 USC §103(a) as being unpatentable over Riebel et al. US 6,284,710.

Claims 24-26 were rejected under 35 USC §112, first paragraph, as lacking enablement for the described indications. Specifically the Examiner astates that the specification does not provide enablement for treating all the diseases embraced in the claim language. In addition to the effect of kinase inhibition on angiogenesis, the literature correlating kinase inhibition and disease state modification is vast. Representative examples are described below and submitted in a separate Supplemental Infvention Disclosure Statement.

Kinase	disease	references
1. EGFR-1	polycystic kidney disease	Sweeney, et al., Kidney Int., 57, 33-40 (2000)
	Cancer	Raymond, et al., Drugs, 60, S1, 15-23 (2000)
2. IGFR-1	cancers	Khandwala et al., Endocrine Rev., 21(3) 215-244 (2000).
3. MET-1	cancer	Cao et al., Proc. Nat. Acad. Sci., USA, 98(13), 7443-7448 (2001)
4. LCK-1	autoimmune disease	Kamens, et al., Curr. Opin. in Invest. Drugs 2(9), 1213-1219 (2001).
5. PDGFRB-1	leukemia	Scheijen and Griffin, Oncogene, 21, 3314-3333 (2002)
6. TEK-1	myeloproliferative disorders	Muller, et al., Leukemia Res., 26, 163-168 (2002)
7. ERBB2-2	breast cancer	Artega et al., Sem in Onc., 29, (s11), 4-10 (2002)

The compounds of the present invention have inhibition of the above kinases as described in the specification in Tables 2-5, pages 296-353. Applicants request reconsideration of the 35 USC §112 rejections in view of the above discussion.

Claims 1, 6, 8, 22 and 28-29 were rejected under 35 USC §102(b) as being anticipated by Giraldi et al. US 3,074,943. Applicants request reconsideration of the rejection in view of the amended proviso language in Claim 1 which eliminates compounds of Giraldi et al.

Claims 1, 5-8, 22 and 28-29 were rejected under 35 USC §102(b) as being anticipated by Cutler et al. US 3,097,205. Applicants request reconsideration of the rejection in view of the amended proviso language in Claim 1 which eliminate the compounds of Cutler et al.

Claims 1, 6, 23 and 28-29 were rejected under 35 USC §102(b) as being anticipated by Cutler et al. US 3,209,003. Applicants request reconsideration of the rejection in view of the amended proviso language in Claim 1 which eliminate compounds of Cutler et al.

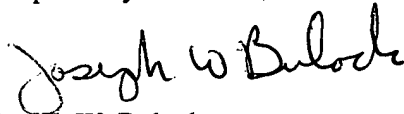
Claims 1, 6 and 8-9 were rejected under 35 USC §103(a) as being unpatentable over Newton et al. US 5,062,882. Newton describes tri-substituted triazines as herbicides (weed killers). The pattern of preferences established by this reference teaches away from the compounds of the current invention. Of the seventy two examples of substituted triazines identified in Newton, only examples 8-9, and 46 did not have di-alkoxy substitution. The biological data described in Table 3 indicates that there was a substantial decrease in activity when R¹ is not methoxy (Examples 8-9) compared with the other compounds. Thus, one skilled in the art would be taught away from the compounds of the present invention. Applicants contend that Newton et al. do not render obvious the disubstituted triazines of the present invention.

Claims 1, and 6 were rejected under 35 USC §103(a) as being unpatentable over Riebel et al. US 6,284,710. Riebel et al. describe triazines as herbicides (weed killers). The compounds of Riebel require the presence of a -NH₂ substituent. Most of compounds made by Riebel and all the compounds tested additionally have haloalkyl or methylthio substitution on the triazine. This indicates that the "Z-substituent" was important for controlling non-specific toxicity, and that haloalkyl and methylthio substituents were most preferred "Z-substituents". Thus Riebel et al. teach away from the disubstituted triazines of the present invention which do not have -NH₂, haloalkyl or alkylthio substitution on the triazine ring. Applicants contend that the '710 patent does not render obvious the disubstituted triazines of the present invention.

In view of the above, none of the references, taken singly or in any combination, describes or suggests compounds of the present invention. Applicants therefore submit that the compounds of the present invention are not obvious in view of the cited prior art.

It is therefore respectfully submitted that Claims 1-29 are now in condition for allowance.
Accordingly, allowance of Claims 1-29 are respectfully solicited.

Respectfully submitted,



Joseph W. Bullock
Attorney for Applicant

Registration No.: 37,103

Phone: 805.447.7966

Date: February 5, 2003

Please send all future correspondence to:

US Patent Operations/ JWBcb

Dept. 430, M/S 27-4-A

AMGEN INC.

One Amgen Center Drive

Thousand Oaks, California 91320-1799

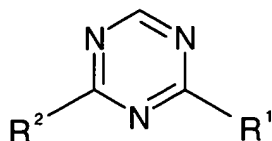
VERSION WITH MARKINGS TO SHOW CHANGES

In the Claims

Cancel claims 8-9, without prejudice.

Amend Claims 1, as follows:

1. (Amended twice) A compound having the formula:



wherein,

Each R¹ and R² is independently R³; R⁸; NHR³; NHR⁵; NHR⁶; NR⁵R⁵; NR⁵R⁶; [SR⁵; SR⁶; SR³; OR⁵; OR⁶; OR³; C(O)R³]; heterocyclyl optionally substituted with 1-4 independent R⁴ on each ring; or C1-C10 alkyl substituted with 1-4 independent R⁴;

Each R³ is independently aryl; phenyl optionally substituted with 1-5 independent R⁴ on each ring; or heteroaryl optionally substituted with 1-4 independent R⁴ on each ring;

Each n is independently 1 or 2;

Each m is independently 0, 1, 2, 3, or 4;

Each R⁴ is independently selected from H, C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R⁸; halo; haloalkyl; SR⁵; OR⁵; OC(O)R⁵; NR⁵R⁵; NR⁵R⁶; NR⁵R¹⁶; COOR⁵; NO₂; CN; C(O)R⁵; C(O)C(O)R⁵; C(O)NR⁵R⁵; S(O)_nR⁵; S(O)_nNR⁵R⁵; NR⁵C(O)NR⁵R⁵; NR⁵C(O)C(O)R⁵; NR⁵C(O)R⁵; NR⁵(COOR⁵); NR⁵C(O)R⁸; NR⁵S(O)_nNR⁵R⁵; NR⁵S(O)_nR⁵; NR⁵S(O)_nR⁸; NR⁵C(O)C(O)NR⁵R⁵; NR⁵C(O)C(O)NR⁵R⁶; OC(O)NR⁵R⁵; OS(O)_nNR⁵R⁵; NR⁵S(O)_nOR⁵; P(O)(OR⁵)₂; C1-C10 alkyl substituted with 1-3 independent aryl, R⁷ or R⁸; or C2-C10 alkenyl substituted with 1-3 independent aryl, R⁷ or R⁸;

Each R⁵ is independently H; C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R⁹; haloalkyl; C1-C10 alkyl substituted with 1-3

independent aryl, R^7 or R^9 groups; C3-C10 cycloalkyl substituted with 1-3 independent aryl, R^7 or R^9 groups; or C2-C10 alkenyl substituted with 1-3 independent aryl, R^7 or R^9 ;

Each R^6 is independently $C(O)R^5$, $COOR^5$, $C(O)NR^5R^5$, $C(=N R^5) NR^5R^5$, or $S(O)_n R^5$;

Each R^7 is independently halo, CF_3 , SR^{10} , OR^{10} , $OC(O)R^{10}$, $NR^{10}R^{10}$, $NR^{10}R^{11}$, $NR^{11}R^{11}$, $COOR^{10}$, NO_2 , CN , $C(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $C(O)NR^{10}R^{10}$, $N(R^{10})C(O)R^{10}$, $N(R^{10})(COOR^{10})$, $S(O)_nNR^{10}R^{10}$; $NR^{10}S(O)_nNR^{10}R^{10}$; $NR^{10}S(O)_nR^{10}$; or $P(O)(OR^5)_2$;

Each R^8 is independently a 3-8 membered monocyclic, 7-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms independently selected from O, N, or S, which may be saturated or unsaturated, and wherein 0, 1, 2, 3 or 4 atoms of each ring may be substituted by a substituent independently selected from C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R^9 ; halo; sulfur; oxygen; CF_3 ; SR^5 ; OR^5 ; $OC(O)R^5$; NR^5R^5 ; NR^5R^6 ; NR^6R^6 ; $COOR^5$; NO_2 ; CN ; $C(O)R^5$; $C(O)NR^5R^5$; $S(O)_nNR^5R^5$; $NR^5C(O)NR^5R^5$; $NR^5C(O)R^9$; $NR^5S(O)_nNR^5R^5$; $NR^5S(O)_nR^9$; C1-C10 alkyl substituted with 1-3 independent R^7 , R^9 or aryl; or C2-C10 alkenyl substituted with 1-3 independent R^7 , R^9 or aryl;

Each R^9 is independently a 3-8 membered monocyclic, 7-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms independently selected from O, N, or S, which may be saturated or unsaturated, and wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent independently selected from C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; halo; sulfur; oxygen; CF_3 ; haloalkyl; SR^{10} ; OR^{10} ; $NR^{10}R^{10}$; $NR^{10}R^{11}$; $NR^{11}R^{11}$; $COOR^{10}$; NO_2 ; CN ; $C(O)R^{10}$; $S(O)_nR^{10}$; $S(O)_nNR^{10}R^{10}$; or $C(O)NR^{10}R^{10}$;

Each R^{10} is independently H; C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; haloalkyl; C1-C10 alkyl optionally substituted with 1-3 independent C1-C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C4-C10 cycloalkenyl, halo, OR^{12} , SR^{12} , $NR^{12}R^{12}$, $COOR^{12}$, NO_2 , CN , $C(O)R^{12}$, $C(O)NR^{12}R^{12}$, $NR^{12}C(O)R^{12}$, $N(R^{12})(COOR^{12})$, $S(O)_nNR^{12}R^{12}$, or $OC(O)R^{12}$; or phenyl optionally substituted with 1-3 independent C1-C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C4-

C10 cycloalkenyl, halo, CF₃, OR¹², SR¹², NR¹²R¹², COOR¹², NO₂, CN, C(O)R¹², C(O)NR¹²R¹², NR¹²C(O)R¹², N(R¹²)(COOR¹²), S(O)_nNR¹²R¹², or OC(O)R¹²;

Each R¹¹ is independently C(O)R¹⁰, COOR¹⁰, C(O)NR¹⁰R¹⁰ or S(O)_nR¹⁰;

Each R¹² is independently H; C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; C1-C10 alkyl substituted with 1-3 independent C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C4-C10 cycloalkenyl, halo, CF₃, OR¹³, SR¹³, NR¹³R¹³, COOR¹³, NO₂, CN, C(O)R¹³, C(O)NR¹³R¹³, NR¹³C(O)R¹³, or OC(O)R¹³; or phenyl optionally substituted with 1-3 independent C1-C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C4-C10 cycloalkenyl, halo, CF₃, OR¹³, SR¹³, NR¹³R¹³, COOR¹³, NO₂, CN, C(O)R¹³, C(O)NR¹³R¹³, NR¹³C(O)R¹³, or OC(O)R¹³;

Each R¹³ is independently H; C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; C1-C10 alkyl optionally substituted with halo, OR¹⁴, SR¹⁴, NR¹⁴R¹⁴, COOR¹⁴, NO₂, CN; or phenyl optionally substituted with halo, CF₃, OR¹⁴, SR¹⁴, NR¹⁴R¹⁴, COOR¹⁴, NO₂, CN;

Each R¹⁴ is independently H; C1-C10 alkyl; C3-C10 cycloalkyl or phenyl;

Each R¹⁶ is independently H, C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R⁸; halo; haloalkyl; COOR⁵; C(O)R⁵; C(O)C(O)R⁵; C(O)NR⁵R⁵; S(O)_nR⁵; S(O)_nNR⁵R⁵; C1-C10 alkyl substituted with 1-3 independent aryl, R⁷, R⁸, or phenyl optionally substituted with substituted with 1-4 independent R²³; or C2-C10 alkenyl substituted with 1-3 independent aryl, R⁷ or R⁸;

Each R²³ is independently selected from H, C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R⁸; halo; haloalkyl; SR⁵; OR⁵; OC(O)R⁵; NR⁵R⁵; NR⁵R⁶; COOR⁵; NO₂; CN; C(O)R⁵; C(O)C(O)R⁵; C(O)NR⁵R⁵; S(O)_nR⁵; S(O)_nNR⁵R⁵; NR⁵C(O)NR⁵R⁵; NR⁵C(O)C(O)R⁵; NR⁵C(O)R⁵; NR⁵(COOR⁵); NR⁵C(O)R⁸; NR⁵S(O)_nNR⁵R⁵; NR⁵S(O)_nR⁵; NR⁵S(O)_nR⁸; NR⁵C(O)C(O)NR⁵R⁵; NR⁵C(O)C(O)NR⁵R⁶; OC(O)NR⁵R⁵; OS(O)_nNR⁵R⁵; NR⁵S(O)_nOR⁵; P(O)(OR⁵)₂; C1-C10 alkyl substituted with 1-3 independent aryl, R⁷ or R⁸; or C2-C10 alkenyl substituted with 1-3 independent aryl, R⁷ or R⁸;

Each haloalkyl is independently a C1-C10 alkyl substituted with one or more halogen atoms, selected from F, Cl, Br, or I, including perhaloalkyl;

Each aryl is independently a 6-carbon monocyclic, 10-carbon bicyclic or 14-carbon tricyclic aromatic ring system optionally substituted with 1-3 independent C1-C10 alkyl;

C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; R⁹; halo; haloalkyl; OR¹⁰; SR¹⁰; NR¹⁰R¹⁰; NR¹⁰R¹¹; COOR¹⁰; NO₂; CN; C(O)R¹⁰; C(O)C(O)R¹⁰; C(O)NR¹⁰R¹⁰; N(R¹⁰)C(O)NR¹⁰R¹⁰; N(R¹⁰)C(O)R¹⁰; N(R¹⁰)S(O)_nR¹⁰; N(R¹⁰)(COOR¹⁰); NR¹⁰C(O)C(O)R¹⁰; NR¹⁰C(O)R⁹; NR¹⁰S(O)_nNR¹⁰R¹⁰; NR¹⁰S(O)_nR⁹; NR¹²C(O)C(O)NR¹²R¹²; S(O)_nR¹⁰; S(O)_nNR¹⁰R¹⁰; OC(O)R¹⁰; C1-C10 alkyl substituted with 1-3 independent R⁹, halo, CF₃, OR¹⁰, SR¹⁰, OC(O)R¹⁰, NR¹¹R¹¹, NR¹⁰R¹⁰, NR¹⁰R¹¹, COOR¹⁰, NO₂, CN, C(O)R¹⁰, OC(O)NR¹⁰R¹⁰, C(O)NR¹⁰R¹⁰, N(R¹⁰)C(O)R¹⁰, N(R¹⁰)(COOR¹⁰), S(O)_nNR¹⁰R¹⁰; R¹⁰; or C2-C10 alkenyl substituted with 1-3 independent R⁹, halo, CF₃, OR¹⁰, SR¹⁰, OC(O)R¹⁰, NR¹¹R¹¹, NR¹⁰R¹⁰, NR¹⁰R¹¹, COOR¹⁰, NO₂, CN, C(O)R¹⁰, OC(O)NR¹⁰R¹⁰, C(O)NR¹⁰R¹⁰, N(R¹⁰)C(O)R¹⁰, N(R¹⁰)(COOR¹⁰), S(O)_nNR¹⁰R¹⁰;

Each heterocyclyl is independently a 3-8 membered nonaromatic monocyclic, 8-12 membered nonaromatic bicyclic, or 11-14 membered nonaromatic tricyclic, ring system having 1-4 heteroatoms if monocyclic, 1-8 heteroatoms if bicyclic, or 1-10 heteroatoms if tricyclic, said heteroatoms independently selected from O, N, or S;

Each heteroaryl is independently a 5-8 membered aromatic monocyclic, 8-12 membered aromatic bicyclic, or 11-14 membered aromatic tricyclic ring system having 1-4 heteroatoms if monocyclic, 1-8 heteroatoms if bicyclic, or 1-10 heteroatoms if tricyclic, said heteroatoms independently selected from O, N, or S;

provided R¹ and R² are not both 1-alkylpyridinium, or both 4-pyridyl [**or both morpholino**];

further provided neither R¹ or R² is [**not**] morpholino or NH₂;

[further provided R¹ and R² are not both hydroxy, methoxy, ethoxy or phenoxy;

further provided R¹ is not phenoxy, acetlamino, or methylamino when R² is morpholino;

further provided R¹ is not methoxy or hydroxy when R² is 4-chlorophenylamino;

further provided R¹ is not phenoxy, methoxy or ethoxy when R² is 4-aminophenylsulfonylamino;

further provided R¹ is not phenoxy when R² is 4-methylthiophenylamino or sulfanilamido; and

further provided R¹ is not hydroxy when R² is hexylamino, phenylamino, 3-methylphenylamino, 2-ethoxyphenylamino, 4-methylthiophenylamino, 2-

ethylsulfinylphenylamino, 3-propylsulfonylphenylamino, 4-acetylphenylamino, 4-sulfamylphenylamino, 3-nitrophenylamino, 4-cyanophenylamino, 4-carboxyphenylamino, 4-(acetylamino)phenylamino, 4-biphenylamino, 1-naphthylamino, 4-pyridylamino, 2-thiazolylamino, 4-quinolylamino, and 2-pyrimidinylamino].

6. (Amended twice) The compound of claim 1 wherein,

R^1 is independently NHR^5 ;

R^2 is independently NHR^3 ;

Each R^3 is independently aryl; phenyl optionally substituted with 1-5 independent R^4 on each ring; or heteroaryl optionally substituted with 1-4 independent R^4 on each ring;

Each R^4 is independently selected from H, C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R^8 ; halo; CF_3 ; SR^5 ; OR^5 ; $OC(O)R^5$; NR^5R^5 ; NR^5R^6 ; NR^5R^{16} ; $COOR^5$; NO_2 ; CN; $C(O)R^5$; $C(O)C(O)R^5$; $C(O)NR^5R^5$; $S(O)_nR^5$; $S(O)_nNR^5R^5$; $NR^5C(O)NR^5R^5$; $NR^5C(O)C(O)R^5$; $NR^5C(O)R^5$; $NR^5(COOR^5)$; $NR^5C(O)R^8$; $NR^5S(O)_nNR^5R^5$; $NR^5S(O)_nR^5$; $NR^5S(O)_nR^8$; $NR^5C(O)C(O)NR^5R^5$; $NR^5C(O)C(O)NR^5R^6$; $OC(O)NR^5R^5$; $OS(O)_nNR^5R^5$; $NR^5S(O)_nOR^5$; $P(O)(OR^5)_2$; C1-C10 alkyl substituted with 1-3 independent aryl, R^7 or R^8 ; or C2-C10 alkenyl substituted with 1-3 independent aryl, R^7 or R^8 ;

Each R^5 is independently H; C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R^9 ; haloalkyl; C1-C10 alkyl substituted with 1-3 independent aryl, R^7 or R^9 groups; C3-C10 cycloalkyl substituted with 1-3 independent aryl, R^7 or R^9 groups; or C2-C10 alkenyl substituted with 1-3 independent aryl, R^7 or R^9 ;

Each R^6 is independently $C(O)R^5$, $COOR^5$, $C(O)NR^5R^5$, $C(=NR^5)NR^5R^5$, or $S(O)_nR^5$;

Each R^7 is independently halo, CF_3 , SR^{10} , OR^{10} , $OC(O)R^{10}$, $NR^{10}R^{10}$, $NR^{10}R^{11}$, $NR^{11}R^{11}$, $COOR^{10}$, NO_2 , CN, $C(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $C(O)NR^{10}R^{10}$, $N(R^{10})C(O)R^{10}$, $N(R^{10})(COOR^{10})$, $S(O)_nNR^{10}R^{10}$; $NR^{10}S(O)_nNR^{10}R^{10}$; $NR^{10}S(O)_nR^{10}$; or $P(O)(OR^5)_2$;

Each R^8 is independently a 3-8 membered monocyclic, 7-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms independently selected from O, N, or S, which may be saturated or unsaturated, and wherein 0, 1, 2, 3 or 4 atoms of each ring may be

substituted by a substituent independently selected from C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R^9 ; halo; sulfur; oxygen; CF_3 ; SR^5 ; OR^5 ; $OC(O)R^5$; NR^5R^5 ; NR^5R^6 ; NR^6R^6 ; $COOR^5$; NO_2 ; CN ; $C(O)R^5$; $C(O)NR^5R^5$; $S(O)_nNR^5R^5$; $NR^5C(O)NR^5R^5$; $NR^5C(O)R^9$; $NR^5S(O)_nNR^5R^5$; $NR^5S(O)_nR^9$; C1-C10 alkyl substituted with 1-3 independent R^7 , R^9 or aryl; or C2-C10 alkenyl substituted with 1-3 independent R^7 , R^9 or aryl;

Each R^9 is independently a 3-8 membered monocyclic, 7-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms independently selected from O, N, or S, which may be saturated or unsaturated, and wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent independently selected from C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; halo; sulfur; oxygen; CF_3 ; haloalkyl; SR^{10} ; OR^{10} ; $NR^{10}R^{10}$; $NR^{10}R^{11}$; $NR^{11}R^{11}$; $COOR^{10}$; NO_2 ; CN ; $C(O)R^{10}$; $S(O)_nR^{10}$; $S(O)_nNR^{10}R^{10}$; or $C(O)NR^{10}R^{10}$;

Each R^{10} is independently H; C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; haloalkyl; C1-C10 alkyl optionally substituted with 1-3 independent C1-C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C4-C10 cycloalkenyl, OR^{12} , SR^{12} , $NR^{12}R^{12}$, $COOR^{12}$, NO_2 , CN , $C(O)R^{12}$, $C(O)NR^{12}R^{12}$, $NR^{12}C(O)R^{12}$, $N(R^{12})(COOR^{12})$, $S(O)_nNR^{12}R^{12}$, or $OC(O)R^{12}$; or phenyl optionally substituted with 1-3 independent C1-C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C4-C10 cycloalkenyl, halo, CF_3 , OR^{12} , SR^{12} , $NR^{12}R^{12}$, $COOR^{12}$, NO_2 , CN , $C(O)R^{12}$, $C(O)NR^{12}R^{12}$, $NR^{12}C(O)R^{12}$, $N(R^{12})(COOR^{12})$, $S(O)_nNR^{12}R^{12}$, or $OC(O)R^{12}$;

Each R^{11} is independently $C(O)R^{10}$, $COOR^{10}$, $C(O)NR^{10}R^{10}$ or $S(O)_nR^{10}$;

Each R^{12} is independently H; C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; C1-C10 alkyl substituted with 1-3 independent C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C4-C10 cycloalkenyl, halo, CF_3 , OR^{13} , SR^{13} , $NR^{13}R^{13}$, $COOR^{13}$, NO_2 , CN , $C(O)R^{13}$, $C(O)NR^{13}R^{13}$, $NR^{13}C(O)R^{13}$, or $OC(O)R^{13}$; or phenyl optionally substituted with 1-3 independent C1-C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C4-C10 cycloalkenyl, halo, CF_3 , OR^{13} , SR^{13} , $NR^{13}R^{13}$, $COOR^{13}$, NO_2 , CN , $C(O)R^{13}$, $C(O)NR^{13}R^{13}$, $NR^{13}C(O)R^{13}$, or $OC(O)R^{13}$;

Each R^{13} is independently H; C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; C1-C10 alkyl optionally substituted with halo, OR^{14} ,

SR¹⁴, NR¹⁴R¹⁴, COOR¹⁴, NO₂, CN; or phenyl optionally substituted with halo, CF₃, OR¹⁴, SR¹⁴, NR¹⁴R¹⁴, COOR¹⁴, NO₂, CN;

Each R¹⁴ is independently H; C1-C10 alkyl; C3-C10 cycloalkyl or phenyl;

Each R¹⁶ is independently H, C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R⁸; halo; CF₃; COOR⁵; C(O)R⁵; C(O)C(O)R⁵; C(O)NR⁵R⁵; S(O)_nR⁵; S(O)_nNR⁵R⁵; C1-C10 alkyl substituted with 1-3 independent aryl, R⁷, R⁸, or phenyl optionally substituted with substituted with 1-4 independent R²³; or C2-C10 alkenyl substituted with 1-3 independent aryl, R⁷ or R⁸; and

Each R²³ is independently selected from H, C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R⁸; halo; CF₃; SR⁵; OR⁵; OC(O)R⁵; NR⁵R⁵; NR⁵R⁶; COOR⁵; NO₂; CN; C(O)R⁵; C(O)C(O)R⁵; C(O)NR⁵R⁵; S(O)_nR⁵; S(O)_nNR⁵R⁵; NR⁵C(O)NR⁵R⁵; NR⁵C(O)C(O)R⁵; NR⁵C(O)R⁵; NR⁵(COOR⁵); NR⁵C(O)R⁸; NR⁵S(O)_nNR⁵R⁵; NR⁵S(O)_nR⁵; NR⁵S(O)_nR⁸; NR⁵C(O)C(O)NR⁵R⁵; NR⁵C(O)C(O)NR⁵R⁶; OC(O)NR⁵R⁵; OS(O)_nNR⁵R⁵; NR⁵S(O)_nOR⁵; P(O)(OR⁵)₂; C1-C10 alkyl substituted with 1-3 independent aryl, R⁷ or R⁸; or C2-C10 alkenyl substituted with 1-3 independent aryl, R⁷ or R⁸;

provided neither R¹ nor R² is [not] NH₂.

22. A composition comprising a compound of any of claims 1-7 and 10-21 [1-21] and a pharmaceutically acceptable carrier.

24. (Amended twice) A method of treating kinase-mediated disease or disease symptoms in a mammal comprising administration of a composition comprising an effective amount of a compound of any of claims 1-7 and 10-21 [1-21].

25. (Amended twice) A method of inhibiting kinase activity in a mammal comprising administration of a composition comprising an effective amount of a compound of any of claims 1-7 and 10-21 [1-21].

26. (Amended twice) A method of treating disease or disease symptoms in a mammal comprising administration of a composition comprising an effective amount of a compound of any of claims 1-7 and 10-21 **[1-21]**.

27. (Amended twice) A method of inhibiting angiogenesis or vasculogenesis activity in a mammal comprising administration of a composition comprising an effective amount of a compound of any of claims 1-7 and 10-21 **[1-21]**.

Add new Claims as follows:

--32. A method of treating cancer comprising administration of a composition comprising an effective amount of a compound of any of claims 1-7 and 10-21.--

--33. A method of treating myeloproliferative disorders comprising administration of a composition comprising an effective amount of a compound of any of claims 1-7 and 10-21.--

--34. A method of treating autoimmune disorders comprising administration of a composition comprising an effective amount of a compound of any of claims 1-7 and 10-21.--

--35. A method of treating polycystic kidney disease comprising administration of a composition comprising an effective amount of a compound of any of claims 1-7 and 10-21.--